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09/751,299	12/28/2000	Mark Madden	DIVER1440-2	8629

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EXAMINER

KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/17/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/751,299

Applicant(s)

MADDEN ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) 18-21 and 25-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17, 22-24 and 31-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachments

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9, 13, 14.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 15, mailed on September 5, 2002), Applicants filed an election and amendment received on January 23, 2003 (Paper No. 16). Said amendment added new claims 31-37. Thus, Claims 1-37 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group I, Claims 1-17 and 22-24, drawn to methods of making α -substituted carboxylic acids using nitrilases, in Paper No. 16 is acknowledged. Applicants also elected production of 2-chloro mandelic acid, using the polypeptide of SEQ ID NO:4, and NH_4Cl for the ammonia source. The traversal is on the ground(s) that "after a complete search directed to making 2-substituted carboxylic acids, it would not be an undue burden for the Patent office to also do a complete search for the corresponding product". This is not found persuasive because the search for the carboxylic acid is wholly distinct from the search for the method of making it since, as previously noted, the carboxylic acid can be made by other means. Applicants requested rejoinder; however, this is improper. Rejoinder is the examination of method claims drawn to making or using a particular product when the product is found allowable; in the instant case, Applicants have elected method claims – no rejoinder will follow.

Applicants also argue that after a complete search of the method using SEQ ID NO:4, a search of all the polypeptides and nucleic acids according to SEQ ID NOs:1/2 and 3/4 would not be undue. The Examiner disagrees. A search for nucleic acid sequences and polypeptides are

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distinct from each other and distinct from the claimed methods for the reasons previously stated.

To join them would present an undue search burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Newly added Claims 31-37 are drawn to the elected invention. Claims 18-21 and 25-30 are withdrawn from consideration as non-elected inventions. Thus, Claims 1-17, 22-24, and 31-37 will be examined herein. Moreover, all species are examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/173,609 and 60/254,414 filed on December 29, 1999 and December 7, 2000, respectively, as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statements filed on September 10, 2001 (Paper No. 9) and July 23, 2002 (Paper N. 14) have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

5. The information disclosure statement filed on July 22, 2002 (Paper No. 13) fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

- a) Other Document AJJ. No copy of Fournard *et al.* was filed.
- b) Other Document AKK: No copy of Gabriel *et al.* was filed.

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- c) Other Document APP: No official copy of Kim *et al.* was filed.
- d) Other Document AUU: The citation of Nagasawa *et al.* is incomplete without a journal title.
- e) Other Document AVV: The citation of Ogawa *et al.* is incomplete.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods for Producing α -Substituted Carboxylic Acids using Nitrilases and Strecker Reagents---

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of use of the Strecker reagents, noting them by particular name, for completeness. Appropriate correction is required.

8. The specification is objected to for the following informalities:

- a) On page 2, in the reaction scheme, the final compound requires an $\text{---NH}_2\text{---}$ not the "NH" as written.
- b) On page 54, line 23, the pending application must be updated to its patent number.
- c) On page 56, line 25, the pending application must be updated to its patent number.

Appropriate correction is required.

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9. The specification is objected to for inappropriate notation of an internet address. On pages 67, 68, and 74, numerous internet addresses are cited in an unacceptable form. See M.P.E.P. § 07.05(e) for the acceptable notation of an internet address. Appropriate correction is required.

10. The specification is objected to for being confusing on page 73, line 30. Therein, Figure 3 is referred to; however, the instant application was filed without drawings. Correction and/or explanation are required.

11. The specification is objected to for being confusing in its reference to component number. Beginning on page 63 and throughout the remainder of the specification, component numbers, like on page 63, line 24, "computer system 100", are noted. These references are confusing in the absence of a diagram of them. Correction and/or explanation are required.

Claim Objections

12. Claim 10 is objected to for depending from itself. Said claim appears to appropriately depend from Claim 8 and will be examined as it this change has been made. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-17, 24, and 31-37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

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applicant regards as the invention. The term “nitrilase or a polypeptide having nitrilase activity” is unclear in view of the different enzymes named nitrilases known in the art. Attached is a description of nitrilase EC 3.5.5.1 and nitrilase EC 4.2.1.84; it is unclear if both of these are intended or if just one (if so, which one) is intended to be included in the scope of the claims. Clarification is required.

14. Claims 2-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the structure, the meaning of the “*” by the center “C” is unclear. Clarification is required.

15. Claims 2-4, 6, 8, 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “optionally R1 and R2 are linked to cooperate to form a functional cyclic moiety” is wholly unclear. What function? What is the meaning of cooperation? Clarification is required.

16. Claims 22-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases “amino acid sequence as set forth in SEQ ID NO:2 or SEQ ID NO:4”, “a nucleic acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3” are unclear in view of the description in the specification. Typically in the art, these phrases clearly mean the structure that is SEQ ID NO:2, for example. However, on pages 61 and 62, the definition of

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these terms is noted to also include sequences “substantially identical thereto” and/or fragments.

The intended meaning of the phrases must be clarified for the record. The Examiner will examine the instant claims as if the definitions are as found in the art, exactly SEQ ID NO:2, for example.

17. Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In step (c), the antecedent basis of the “intermediate of step (a)” is wholly unclear since no intermediates are mentioned in step (a). Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1-17, 24, and 31-37 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods of making α -carboxylic acids using nitrilases wherein either no structure or limited structure (Claim 24) is noted to distinguish the nitrilases applicable to the instant claims.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a

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precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, two nitrilases are described; SEQ ID NOs: 1 and 3 are the DNAs encoding SEQ ID NOs: 2 and 4. In the sequence listing, these sequences are defined as being obtained from an unknown environmental sample. It can be inferred from Example 1 and the sequence listing that the proteins were isolated from an environmental sample, sequenced, used to probe for DNA sequences that were then made recombinantly and expressed in a *Pseudomonas* host (these are all techniques well known in the art). No description of how the structures of these nitrilases affect a productive method is noted in the specification. Thus, one of skill in the art would be unable to identify the structures of other nitrilases useful in the claimed methods by virtue of the instant disclosure.

In view of the large genus of Claim 24, even the limited structure in combination with the broad function is not adequately described in view of the specification as originally filed because it is wholly unclear from the specification what characteristic structure of the nitrilase sequence

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is necessary and/or sufficient in the genus of nitrilases to practice the claimed methods.

Therefore, claims drawn to methods of using the genus of nitrilases are not adequately described.

Additionally, no specific description of making D-phenylalanine, L-methylphenylglycine, L-tert-leucine, D-alanine, or D-hydroxynorleucine is described in the instant specification. No specific description of making (S)-cyclohexylmaleic acid, mandelic acid, or 2-chloro mandelic acid is described in the instant specification. No description of their starting α -aminonitrile or cyanohydrin products is noted. Moreover, no description of the nitrilases to be used in the methods is found. The only example described uses benzaldehyde to make phenylglycine. No generalities are offered so that one of skill in the art could discern that content of the lacking description. Thus, claims to making these particular α -substituted carboxylic acids lack adequate written description in the specification as originally filed.

19. Claims 5, 7-10, and 22-24 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The enablement of the instant methods relies on the identification of nitrilases that perform the proper hydrolysis reaction on the proper substrate to produce, for example, D-phenylalanine. Such identification would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

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experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The only example in the specification is on pages 77-78. Therein, benzaldehyde, KCN, and NH₄Cl are combined to produce phenylglycinonitrile, a chiral α -amino nitrile compound; this is by a known reaction (Strecker reaction). No mention of its stereochemistry is noted, although the Strecker reaction is known to produce racemic mixtures of chiral products. The phenylglycinonitrile (R/S) is added to cell lysates BD1911 and BD1921; no identification of these lysates as containing SEQ ID NOs: 2 or 4 is described. Upon reaction with the lysates, products are assayed by HPLC, but no description of the products is offered. By virtue of the entire description, the product can be assumed to be phenylglycine, a chiral compound. However, the ability of the lysates to produce enantiomerically pure phenylglycine is wholly unfounded in the specification as originally filed. Generally, in the art, when neither (R) nor (S) is specified (as is the case in the instant application), the products are *not* enantiomerically pure.

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The predictability of practicing the instant methods effectively is wholly absent in view of the disclosure.

Claims 22-23. In part, the shortfalls noted above seem to be omissions in the description as originally filed. If BD1911 and BD1921 are lysates of recombinantly expressed SEQ ID NOs:2 and 4 and if the phenylglycine produced in Example 1 is enantiomerically pure D-phenylglycine, Applicants can submit a declaration attesting to said facts and methods using any of SEQ ID NOs:1-4 to make enantiomerically pure D-phenylglycine would be enabled.

Claim 24. Additionally, variation of the nitrilase (Claim 24) is not enabled for use in producing enantiomerically pure D-phenylglycine. The breadth of Claim 24 is enormous. No working examples or guidance concerning the variation of either SEQ ID NOs: 2 or 4 is described. One of skill in the art would be wholly unable to predict regions in the enzymes available for variation with retention of the nitrilase activity. Thus, Claim 24 is not enabled to the full extent of its scope.

Claims 5 and 7. In the absence of definition of the nitrilase, the instant claims are also not enabled to the full extent of their scope for using **any** nitrilase to produce the named amino acids. Copious amounts of experimentation would be required to either find or engineer other nitrilases to produce particular α -substituted amino acid. The specification provides no guidance or working examples for the production of such nitrilases. The state of the prior art is such that numerous nitrilases that use aminonitriles as substrates to produce amino acids are known (see art rejections below), but none specifically to produce those amino acids noted in Claims 5 and 7. The predictability of finding or engineering other nitrilases to produce specific α -substituted amino acid is extremely low considering the state of the art and the instant disclosure. Thus,

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using **any** nitrilase to produce **specific** α -substituted carboxylic acid is not enabled to the full extent of its scope.

Claims 8-10. In the absence of definition of the nitrilase, the instant claims are also not enabled to the full extent of their scope for using **any** nitrilase to produce **any** hydroxy acid. Copious amounts of experimentation would be required to either find or engineer other nitrilases to produce any α -substituted hydroxy acid. The specification provides no guidance or working examples for the production of such nitrilases. The state of the prior art is such that no examples of nitrilases that produce α -substituted hydroxy acids are known. The predictability of finding or engineering other nitrilases to produce any α -substituted hydroxy acid is extremely low considering the state of the art and the instant disclosure. Thus, using **any** nitrilase to produce **any** α -substituted hydroxy acid is not enabled to the full extent of its scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1-4, 6, 11-17, 31, and 33-36 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Wakamoto et al.** (USPN 5,587,303, see IDS Paper No. 13) as evidenced by **Iyer et al.** (Asymmetric catalysis of the Strecker amino acid synthesis by a cyclic dipeptide. *Amino Acids* (1996) 11(304), 259-268). The instant claims are drawn to methods of making

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enantiomerically pure α -substituted amino acids using the Strecker synthesis (aldehyde/ketone, cyanide, and ammonia) coupled to nitrilase hydrolyzing activity.

Wakamoto *et al.* teach production of α -aminonitriles using the Strecker process; such α -aminonitriles are depicted in formula (I) (see column 11, lines 35-40). Wakamoto *et al.* further teach the contact of said α -aminonitriles with microorganisms or enzyme extracts thereof having nitrile-hydrolyzing activity (see column 13, lines 12-17). This contact produces the corresponding L-amino acids (see Tables 4, 16, 19, 21, 24, 25, 29, and 31-40) with enantiomeric purity, such as the production of L-phenylalanine and L-valine. Wakamoto *et al.* does not particularly teach the specifics of the well-known Strecker process.

Iyer *et al.* teach the Strecker process as reacting cyanide with an aldehyde or ketone and ammonia to produce aminonitriles (see page 260, Scheme 1). Iyer *et al.* also teach well-known variations of the Strecker process such as using potassium cyanide (KCN) (an alkali cyanide), ethyl aluminum cyanide (Et_2AlCN) (a metal cyanide), and sodium cyanide (NaCN) (see page 261, Scheme 3).

21. Claim 32 is rejected under 35 U.S.C. § 102(b) as being anticipated by **Wakamoto *et al.*** (USPN 5,587,303, see IDS Paper No. 13). The instant claim is drawn to methods of making α -substituted amino acids using aminonitriles and a nitrilase enzyme.

Wakamoto *et al.* teach the contact of α -aminonitriles with microorganisms or enzyme extracts thereof having nitrile-hydrolyzing activity (see column 13, lines 12-17). This contact produces the corresponding L-amino acids (see Tables 4, 16, 19, 21, 24, 25, 29, and 31-40) with enantiomeric purity.

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22. Claims 32 and 37 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Bhalla et al.** (see IDS Paper No. 13). The instant claim is drawn to methods of making α -carboxylic (amino) acids by reacting an amino nitrile and a nitrilase in a single reaction vessel.

Bhalla et al. teach the reaction of various α -amino nitriles with a nitrilase from *Rhodococcus* (see page 186, Table 1) to produce their corresponding amino acids (see Abstract).

Conclusion

23. Claims 1-17, 22-24, and 31-37 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK

April 15, 2003

